Surgical Manual for the administration of LUXTURNA®▼

IMPORTANT

This medicine contains a genetically modified organism.

Only surgeons experienced in performing macular surgery who undergo the voretigene neparvovec Surgical Education Program in subretinal injection procedures should administer voretigene neparvovec.

The information in this manual is correct as of November 2020. If you have questions about the preparation of voretigene neparvovec, please contact your Novartis representative.

▼This medicinal product is subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk profile of the medicinal product. All suspected adverse reactions should be reported to HPRA Pharmacovigilance at www.hpra.ie. Adverse events can also be reported to Novartis preferably at www.novartis.com/report, by emailing drugsafety.dublin@novartis.com or by calling (01) 2080 612.

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Contents

Purpose of the Surgical Manual

Voretigene neparvovec is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.

This Surgical Manual describes the materials and procedures necessary to perform subretinal injection of voretigene neparvovec.

The purpose of this educational programme is to ensure the correct use of LUXTURNA® in order to minimise the risks associated with its administration and/or the administration procedure.

These risks include:

- increased intraocular pressure
- retinal tear
- retinal detachment
- macular disorders
- cataracts
- intraocular inflammation and/or infection related to the procedure
- accidental exposure to genetically modified organisms
- vitreous opacities

Voretigene neparvovec must only be administered by subretinal injection, performed after a standard 3-port Pars Plana Vitrectomy (PPV).

This manual does not describe procedures for performing standard 3-port Pars Plana Vitrectomy (PPV).

Only surgeons experienced in performing macular surgery who undergo the voretigene neparvovec Surgical Education Program in subretinal injection procedures should administer voretigene neparvovec.

This manual does not describe pharmacy procedures for preparing voretigene neparvovec for administration. Please consult the voretigene neparvovec Pharmacy Manual for more information about pharmacy procedures for preparing voretigene neparvovec.

Required Materials

The treatment center should have standard equipment and supplies used in vitreoretinal surgery available in the operating room on the day of the procedure. All materials required for a standard PPV are to be provided by the treatment center. In addition to these standard materials, the treatment center must also supply the items listed below and described further in following sections:

- Subretinal injection cannula (with a polyamide micro tip with an inner diameter of 41 gauge).
- Extension tube (made of polyvinyl chloride no longer than 6” (15.2cm) in length and with an inner diameter no greater than 1.4mm).
- Two sterile syringes containing diluted voretigene neparvovec (1 primary syringe and a second back-up syringe to be provided by the pharmacy).

Subretinal injection cannula

Table 1 lists subretinal injection cannulas that have been tested in biocompatibility experiments for use with voretigene neparvovec. Each of these cannulas were commercially available as of the date of this manual.

Figure 1 shows a representative subretinal injection cannula.

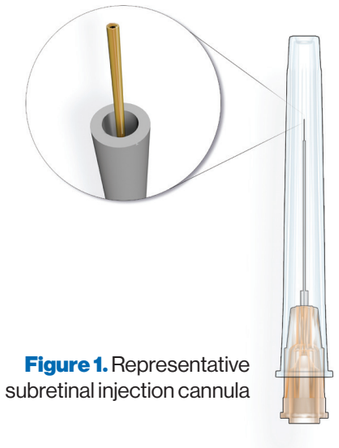

Figure 1. Representative subretinal injection cannula

Table 1. Biocompatible subretinal injection cannulas

Product description	Manufacturer	Reference number
PolyTip® cannula 25 g/38 g* 25 g x 28 mm cannula with 38 g (0.12 mm) x 5 mm tip	**MedOne Surgical, Inc.** Sarasota, FL	**3219**
De Juan/Awh subretinal injection cannula 25 g/41 g 41 g (0.10 mm) tip	**Synergetics, Inc. USA - Bausch & Lomb, Inc.** O’Fallon, MO	**12.03.25**

* Inner diameter 41g (gauge).

- A back-up subretinal injection cannula should be available for each administration of voretigene neparvovec.
- Ensure the subretinal injection cannula instrument gauge is no larger than the trocar size to be used in the PPV.

Extension tube

Table 2 lists extension tubes that have been tested in biocompatibility experiments for use with voretigene neparvovec. Each of the listed extension tubes was commercially available as of the date of this manual.

Figure 2 shows a representative extension tube.

Table 2. Biocompatible extension tubes

Product description	Manufacturer	Reference number
Ocular irrigation tube 15.2 cm (6”), ID 0.8 mm, OD 1.6 mm male/female Luer lock connections	**Eagle Labs** Rancho Cucamonga, CA	169-30L-6
High pressure extension tube 15.2 cm (6”), ID 1.4 mm, OD 2.29 mm, PVC tube with male and female Luer lock connections	MedOne Surgical, Inc. Sarasota FL	3243

ID= inner diameter; OD= outer diameter.

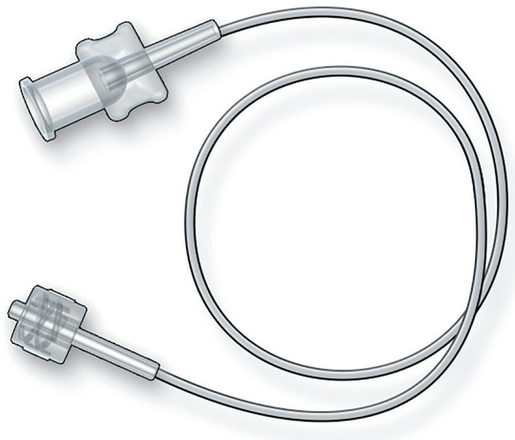

Figure 2. Representative extension tube.

- Use one of the recommended extension tubes. To avoid excess priming volume, do not use a tube longer than 6“ (15.2 cm) or with an ID greater than 1.4 mm.

Syringe

- The pharmacy will prepare 2 syringes of voretigene neparvovec.
- The first syringe will be used to administer the product and the second syringe will serve as a back-up supply.
- Each 1-mL syringe will contain 0.8 mL of voretigene neparvovec.
- Maintain voretigene neparvovec at room temperature until administration.
- Begin administration procedure within 4 hours from the preparation of voretigene neparvovec by the pharmacy.
- Following administration, all materials (including the back-up syringe) should be discarded into a biohazard container.
- Refer to local biosafety guidelines for the handling and disposal of the product.

Table 3 lists a commercially available syringe that has been tested in biocompatibility experiments for use with voretigene neparvovec. This syringe was commercially available as of the date of this manual. Figure 3 shows this syringe.

Table 3. Sterile biocompatible syringe

Product description	Manufacturer	Reference number
BD Luer-Lok™ 1-mL disposable syringe Has 1/100 mL graduations	**Becton, Dickinson & Company** Franklin Lakes, NJ	309628

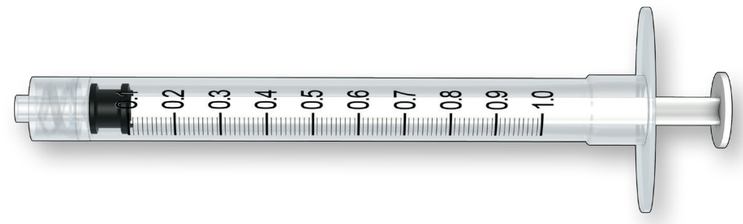

Figure 3. Representative syringe (model shown: BD Luer-Lok™ 1-mL disposable syringe, Franklin Lakes, NJ; reference number 309628)
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Procedure

Preoperative procedures

Immunomodulatory regimen

In addition to standard preoperative and postoperative procedures, subretinal injection of voretigene neparvovec requires administration of an immunomodulatory regimen of prednisone.

Prior to initiation of the immunomodulatory regimen and prior to administration of voretigene neparvovec, the patient must be evaluated for symptoms of active infectious disease of any nature. In case of such infection, the start of the immunomodulatory regimen and subsequent voretigene neparvovec treatment must be postponed until after the patient has recovered.

Starting 3 days prior to the administration of voretigene neparvovec to the first eye, it is recommended that an immunomodulatory regimen is initiated following the schedule outlined in Table 4. Initiation of the immunomodulatory regimen for the second eye should follow the same schedule and supercede completion of the immunomodulatory regimen of the first eye. Patients will be on a systemic immunomodulatory regimen for a minimum of 18 days up to a maximum of 30 days, depending on the timing of the administration of voretigene neparvovec to the second eye.

Table 4. Preoperative and postoperative immunomodulatory regimen for each eye

Preoperative	3 days prior to administration	Prednisone (or equivalent) 1 mg/kg/day (maximum of 40 mg/day)
Postoperative	4 days (including the day of administration)	Prednisone (or equivalent) 1 mg/kg/day (maximum of 40 mg/day)
	Followed by up to 5 days	Prednisone (or equivalent) 0.5 mg/kg/day (maximum of 20 mg/day)
	Followed by 5 days of one dose every other day	Prednisone (or equivalent) 0.5 mg/kg every other day (maximum of 20 mg/day)

Special Precautions for disposal and other handling

Avoid accidental exposure and follow universal biohazard precautions for preparation, administration and handling of voretigene neparvovec.

- Wear personal protective equipment (e.g. laboratory coat, safety glasses, and gloves) while preparing or administering voretigene neparvovec.
- Avoid accidental exposure to voretigene neparvovec, including contact with skin, eyes, and mucous membranes. Cover any exposed wounds before handling.
- Treat all voretigene neparvovec spills with a virucidal agent such as 1% sodium hypochlorite and blot using absorbent materials.
- Dispose of all materials that may have come in contact with voretigene neparvovec (e.g. vial, syringe, needle, cotton gauze, gloves, masks, or dressings) in accordance with universal biohazard precautions.

Accidental exposure

- **In the event of an accidental occupational exposure (e.g. through a splash to the eyes or mucous membranes), flush with clean water for at least 5 minutes.**
- **In the event of exposure to broken skin or needle stick injury, clean the affected area thoroughly with soap and water and/or a disinfectant.**

This medicine contains genetically modified organisms. Unused medicine must be disposed of in compliance with the institutional guidelines for genetically modified organisms or biohazardous waste, as appropriate.

Surgery logistics

The logistics and processes of scheduling surgery, preoperative care, and transportation of voretigene neparvovec from the pharmacy to the operating room, is dependent on timely, efficient and concise communication between all parties.

Once the surgery date and time have been determined, confirm that the surgeon, assistant, operating room staff and pharmacy staff have been informed and are expecting to be available at the designated surgical date and time.

Voretigene neparvovec is a sterile concentrate solution that requires thawing and dilution prior to administration and preparation of voretigene neparvovec should be performed within 4 hours of beginning the administration procedure. Therefore, confirm availability of voretigene neparvovec with the pharmacy at least one day prior to surgery and specify the mode or person transporting voretigene neparvovec from pharmacy to the operating room.

The patient will undergo the preoperative evaluation and assessment by nursing staff and anesthesiology in the fashion customary for outpatient eye surgery.

IMPORTANT

After the patient has been cleared for surgery by the anesthesiologist, operating room staff calls pharmacy to release the order for product preparation. Do not induce anesthesia before voretigene neparvovec has been prepared and delivered to the operating room.

IMPORTANT

Two syringes (a primary syringe and a second back-up syringe) must be delivered from the pharmacy.

IMPORTANT

Once voretigene neparvovec has been delivered to the operating room, dilate the eye and give adequate anesthesia to the patient.

Surgical team

Subretinal injection of voretigene neparvovec requires coordination between a lead surgeon and an assistant (Figure 4). Effective communication between the surgical team members during the surgical procedure is required to ensure the appropriate administration of voretigene neparvovec. The lead surgeon and the assistant should agree upon communication signals for when to start injecting and when to stop.

- The lead surgeon will have primary responsibility for the procedure, including the following tasks:
  - Inspection of materials
  - Injection apparatus assembly and preparation
  - PPV
  - Preparation of injection site
  - Insertion of the subretinal injection cannula into the retina during the subretinal injection procedure
  - Post-injection procedures
- The assistant will handle the syringe containing voretigene neparvovec during the subretinal injection procedure and control the speed of injection of the drug while the lead surgeon maintains the subretinal injection cannula in the proper position.

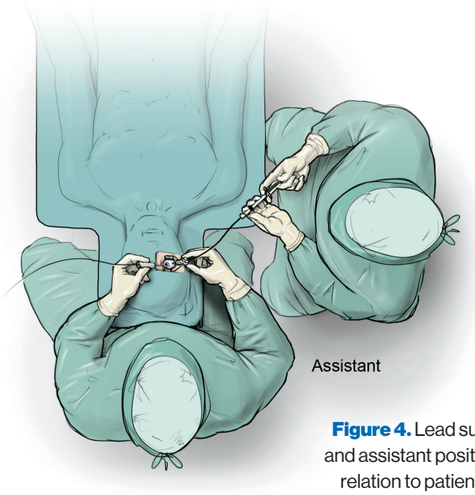

Figure 4. Lead surgeon and assistant positions in relation to patient (view without surgical microscope).

Surgical procedure overview

Method of administration

- Voretigene neparvovec is a single-use vial for a single administration in one eye only.
- Voretigene neparvovec must not be administered by intravitreal injection.
- Voretigene neparvovec is administered as a subretinal injection after vitrectomy in each eye.
- Voretigene neparvovec should not be administered in the immediate vicinity of the fovea to maintain foveal integrity
- The administration of voretigene neparvovec should be carried out in the surgical suite under controlled aseptic conditions to minimise the risk of post operative endophthalmitis.
- Once availability of voretigene neparvovec from the pharmacy is confirmed, adequate anaesthesia should be given to the patient prior to the procedure.
- The eye to be injected must be dilated, and a broad-spectrum microbiocide should be topically administered prior to the surgery according to standard medical practice.
- Intraocular pressure should be monitored prior to, and following administration of voretigene neparvovec, and managed appropriately.

Inspection of materials

1 In the operating room and prior to use, the lead surgeon should inspect the packaging of the subretinal injection cannula and the extension tube to ensure that sterility has not been compromised and the contents have not been damaged. If the tip of the cannula has been deformed, a new subretinal injection cannula must be used.

2 Prior to administration, the lead surgeon should inspect the voretigene neparvovec contained within both syringes (primary syringe and second back-up syringe). If particulates, cloudiness, or discoloration are visible, do not use the product.

CAUTION

In the event that the subretinal injection cannula is damaged or compromised, DO NOT use the damaged cannula. Instead, inspect the back-up subretinal injection cannula and, if not damaged or compromised, use the back-up subretinal injection cannula for the procedure.

Injection apparatus
assembly and preparation

Within the sterile field, connect the syringe containing the diluted voretigene neparvovec to the extension tube and subretinal injection cannula (Figure 5). Then inject voretigene neparvovec slowly through the extension tube and subretinal injection cannula to eliminate any air bubbles.

Preparation of materials in the sterile field

1 On the sterile field, remove the subretinal injection cannula from its packaging and place on the sterile drape, leaving the clear plastic sheath covering the cannula tip in place.

2 Remove the extension tube from its packaging and place on the sterile drape.

3 Remove both syringes containing voretigene neparvovec from the sterile plastic bag and place them on the sterile drape.

Assembly of the components

1 Attach the male end of the extension tube to the subretinal injection cannula, leaving the clear plastic sheath covering the cannula in place (Figure 5).

2 Attach primary syringe containing voretigene neparvovec to the female hub of the extension tube.

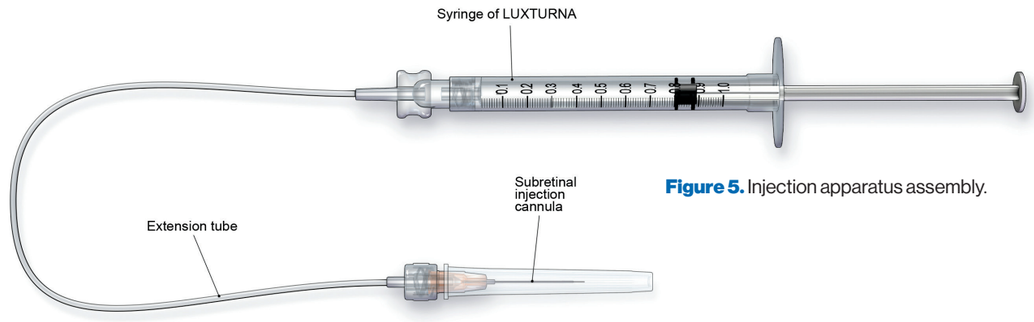

Figure 5. Injection apparatus assembly.

Filling of the subretinal injection cannula
in the sterile field over the sterile drape

1 Remove the plastic sheath from the tip of the subretinal injection cannula. Take care to avoid excess manipulation of the unsheathed cannula tip to avoid cannula deformation or damage.

2 Position the cannula tip over a sterile biosafety waste container.

3 Hold the syringe vertically with the hub positioned upward, and inject voretigene neparvovec slowly through the extension tube and the subretinal injection cannula to eliminate air bubbles. Continue injecting until 0.3 mL of voretigene neparvovec remains in the syringe, and the extension tube and the subretinal injection cannula are completely void of air. Local biosafety guidelines for preparation, administration and handling of voretigene neparvovec should be followed (Figure 6).

4 Confirm the volume of product available in the syringe for injection, by aligning the plunger tip with the line that marks 0.3 mL.

5 Store the filled subretinal injection cannula in a sterile location until the time of subretinal injection.

IMPORTANT

Begin administration procedure within 4 hours from the preparation of voretigene neparvovec by the pharmacy.

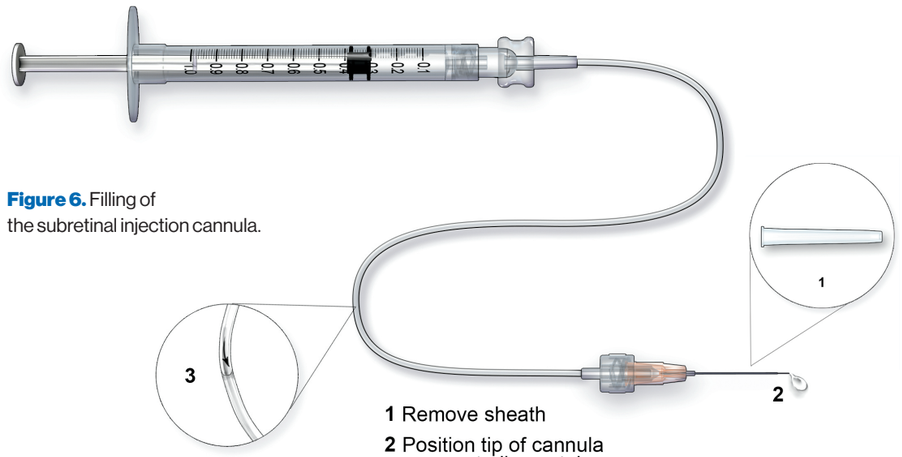

Figure 6. Filling of the subretinal injection cannula.

1 Remove sheath
2 Position tip of cannula over a sterile container
3 Expel contents of syringe until 0.3 mL of drug remains in the syringe

Pars Plana Vitrectomy (PPV)

IMPORTANT

Avoid use of valved trocars to prevent damage to the subretinal injection cannula tip and to help prevent an increase in intraocular pressure (IOP) during the subretinal injection. If valved trocars are used, consider removing the valve cap of the trocar before insertion of the subretinal injection cannula.

1 Perform a 3-port PPV per the standard of care.

2 Trocar placement is standard of care for macular surgeries.

IMPORTANT

Ensure that the vitreous is removed as completely as possible, particularly in the area of superior sclerotomy sites. Vitreous base removal with scleral depression is not necessary.

3 Induce a posterior vitreous detachment and assure that the posterior cortical vitreous is removed by standard means.

Preparation of injection site

Injection site inspection and preparation

1 Inspect the macular region and intended injection site.

2 Using a Membrane Scraper ensure that no vitreous remains over the macula or at the injection site.

3 If a visible epiretinal membrane (ERM) is present, the ERM should be removed according to standard procedures prior to subretinal injection.

IMPORTANT

No dyes or triamcinolone were used to aid vitreous visualization or ERM removal during clinical trials of voretigene neparvovec.

Injection site selection

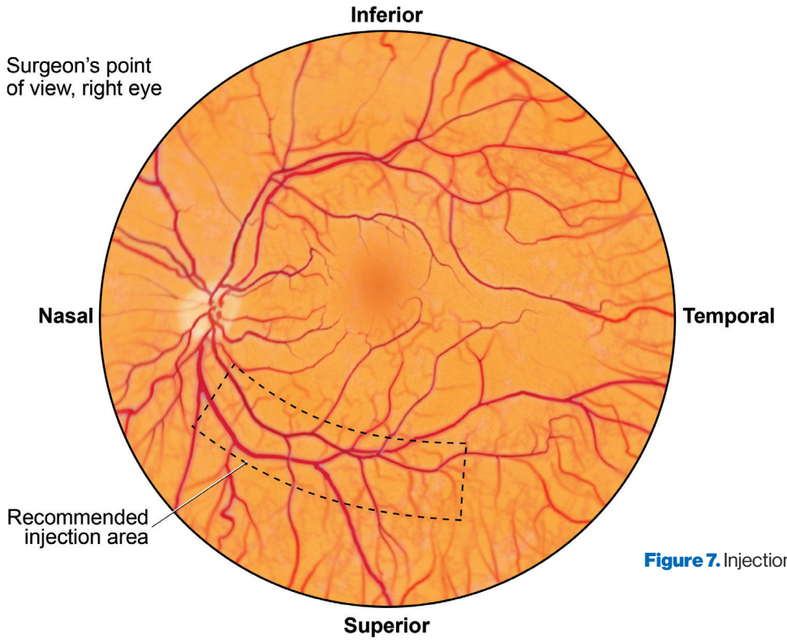

Figure 7. Injection area.

IMPORTANT

The injection site should be located along the superior vascular arcade, at least 2 mm distal to the centre of the fovea (Figure 7).

1 To determine the subretinal injection site location, consider the patient's retinal pathology and anatomy, and the ease of injection site accessibility.

2 The injection site should not be located within areas of pathologic or anatomic features, such as:

- Intraretinal pigment migration
- Dense atrophy.

3 Avoid direct contact with the retinal vasculature to limit risk of injury to retinal arteries/arterioles and to prevent bleeding complications.

Subretinal injection procedure

1 Reduce the IOP to 10 mmHg to accommodate the additional intraocular volume (0.3 mL) of voretigene neparvovec.

2 The assistant should retrieve the injection assembly from the sterile drape and, retaining hold of the syringe, hand the subretinal injection cannula to the lead surgeon.

3 Ensure that the subretinal injection cannula and the syringe containing voretigene neparvovec are each properly locked to the extension tube.

4 Confirm that the tip of the plunger in the syringe is set at 0.3 mL.

5 The lead surgeon should insert the tip of the subretinal injection cannula through the vitrectomy trocar (Figure 8).

6 Under direct visualization, place the tip of the subretinal injection cannula in contact with the retinal surface (Figure 9).

IMPORTANT

Effective and ongoing communication between the lead surgeon and assistant is important to procedural success.

IMPORTANT

Take care not to bend the tip of the cannula during insertion.

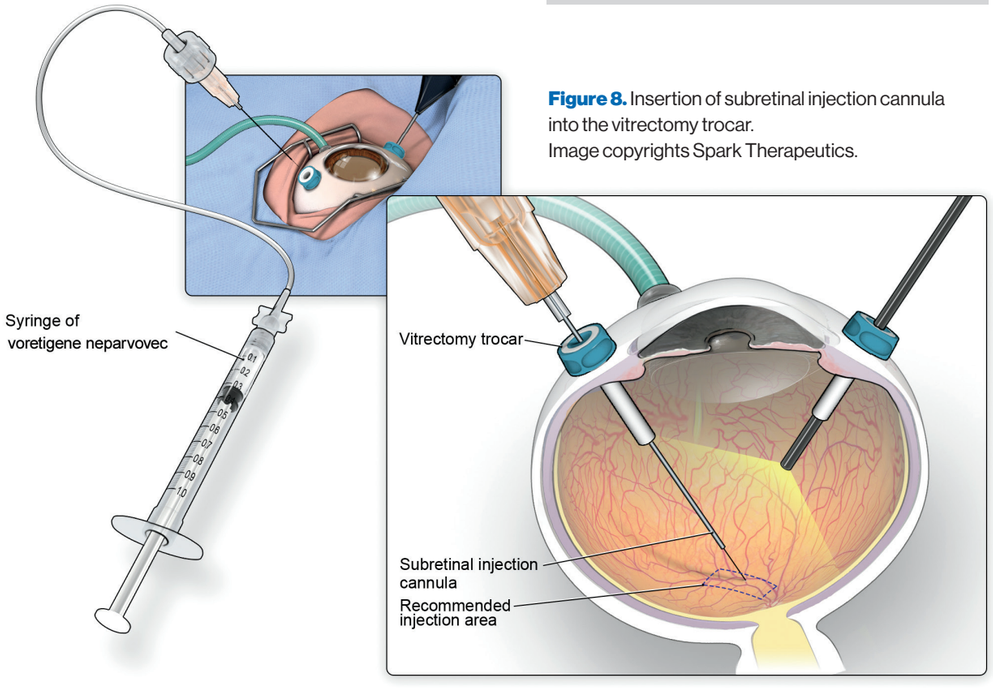

Figure 8. Insertion of subretinal injection cannula into the vitrectomy trocar.
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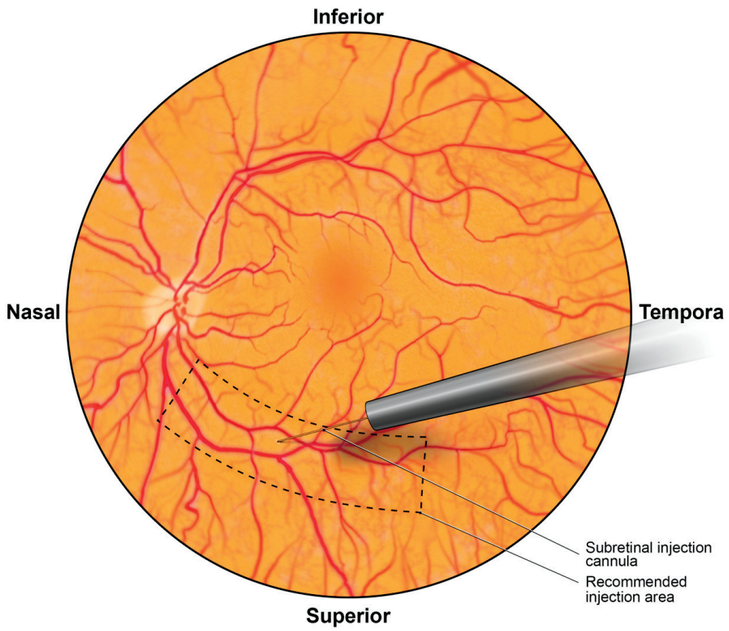


IMPORTANT

The assistant must wait for verbal communication from the lead surgeon before depressing the plunger to initiate the injection.

Figure 9. Subretinal injection cannula approaching injection site.

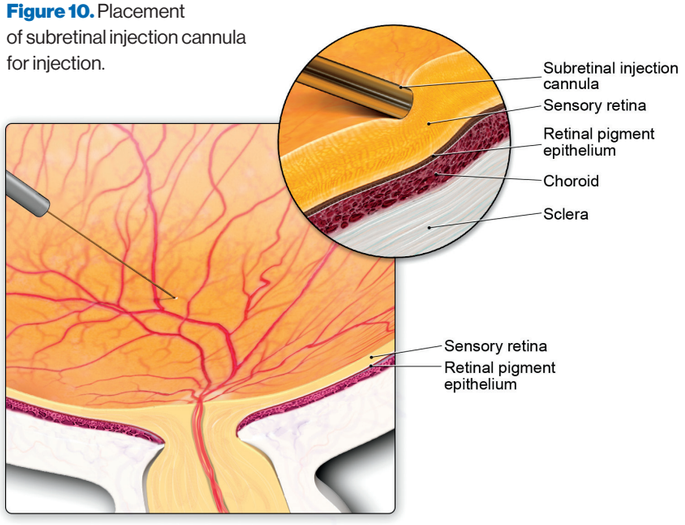
7 Carefully position the tip of the subretinal injection cannula so as to indent the neural retina and drape the retina over the tip of the cannula, taking care not to perforate the retina (Figure 10).

8 The lead surgeon should instruct the assistant to inject a small amount of voretigene neparvovec slowly, until the lead surgeon observes an initial subretinal bleb (Figure 11).

IMPORTANT

Any resistance detected by the assistant while pushing the plunger should be communicated to the lead surgeon. Resistance may indicate a blockage in the injection apparatus assembly or misplacement of the cannula tip.

Figure 10. Placement of subretinal injection cannula for injection.



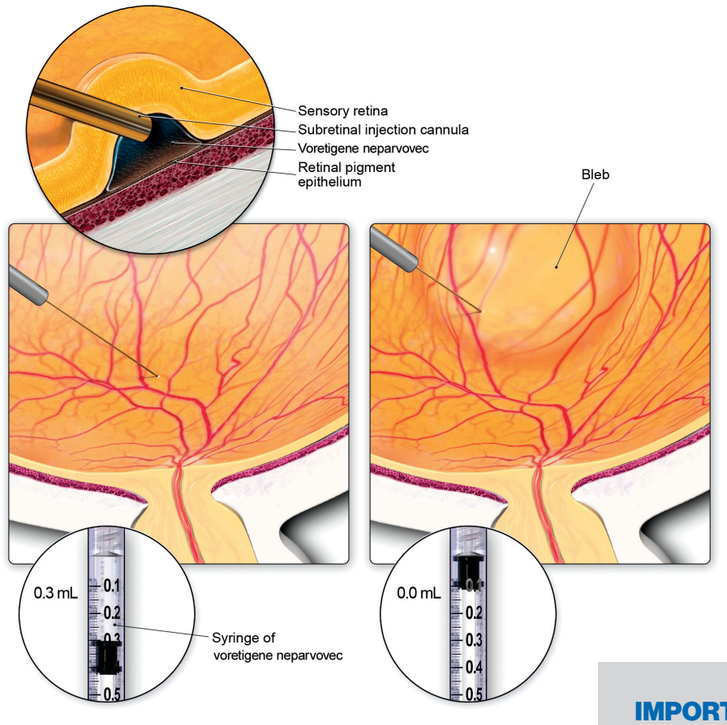


Figure 11. Subretinal injection and bleb formation.

9 If a bleb does not begin to form:

- Stop injection and confirm patency of the subretinal injection cannula.
- If patency is confirmed, redirect the cannula tip to a different injection site within the recommended area.
- Attempt subretinal injection of the remaining drug into the new site.

IMPORTANT

In the event of unsuccessful attempts to raise a bleb with the first syringe, the back-up syringe may be required in order to ensure subretinal delivery of the voretigene neparvovec.

10 If a bleb begins to form, continue slowly injecting the full 0.3 mL of voretigene neparvovec. The assistant should hold the plunger down for approximately 5 seconds after completing the injection to ensure that voretigene neparvovec has exited the subretinal injection cannula.

IMPORTANT

The shape of the bleb and the duration of time required for bleb formation will vary among patients.

11 Upon completion of administration, remove the subretinal injection cannula from the eye.

- Following administration, all materials (including the back-up syringe) should be discarded into a biohazard container.

Post-injection procedures

1 Increase IOP to 30 mmHg.

2 Perform a comprehensive retinal examination using indirect ophthalmoscopy, and scleral indentation to evaluate for any retinal abnormalities. Treat any noted abnormalities as per standard of medical care.

3 Perform a fluid-air exchange in the vitreous cavity in order to remove any voretigene neparvovec that may have refluxed from the subretinal injection site (retinotomy) and to provide tamponade. Carefully avoid fluid drainage near the retinotomy created for the subretinal injection.

IMPORTANT

Do not position the tip of the aspiration cannula in the immediate vicinity of the injection site, in order to prevent removal of the drug from the subretinal space.

4 Withdraw all instruments and vitrectomy trocars.

5 Supine head positioning is initiated immediately in the postoperative period and, upon discharge, the patient should be advised to rest in a supine position for 24 hours.

6 Following subretinal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately

7 Counsel the patient and/or carer on the handling precautions required for 14 days after administration. The patient should be advised not donate blood, organs, tissues and cells for transplantation.

References

1. Novartis Europharm Limited (2019) LUXTURNA® Summary of Product Characteristics.

2. Data on File_1. 2019. Study report for a biocompatiblity study conducted assessing the extension tube and MedOne cannula described.

3. Data on File_2. 2019. Study report for a biocompatiblity study conducted assessing a subretinal cannula (De Juan/Awh) and occular irrigation tube described.

4. Data on File_3. 2019. Clinical protocol for a study assessing drug administration and dosing.

5. Data on File_4. 2019. LUXTURNA® Risk Management Plan additional risk minimisation measures including correct pharmacist and surgeon education, and treatment centre requirements.

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